UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/690,647	10/17/00	GREENBERG A	TUV-005.01

HZ12/0921

PATENT GROUP
FOLEY, HOAG & ELIOT LLP
ONE POST OFFICE SQUARE
BOSTON MA 02109-2170

EXAMINER
SCHMIDT, M

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 09/21/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/690,647	GREENBERG, ANDREW S.
	Examiner	Art Unit
	Mary Schmidt	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U S C § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

KATRINA TURNER
PATENT ANALYST

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
18) ☐ Interview Summary (PTO-413) Paper No(s) _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

2. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-14 are drawn to a broad scope of possible MAPK inhibitors: any direct inhibitor, any inhibitor of ERK1 or ERK2 or a JNK, any antisense, triplex or ribozyme. There are many possible compositions which could be considered part of a MAPK pathway in any whole organism as broadly claimed. Although some specific and non-specific inhibitors are known in the art for MAPK pathway genes/proteins, a representative number of species of such inhibitors for any such gene/protein in any organism are not taught by either the specification as filed or the art. Furthermore, the claimed compositions are further limited to their ability to reduce lipolysis in the subject. Neither the art nor the specification as filed teaches a representative number of such compositions which specifically have the ability to inhibit lipolysis.

The specification teaches by way of example sodium salicylate, BRL (after pre-treatment) and PGJ2 (after pre-treatment) in 3T3-L1 adipocytes reduces TNF-alpha induced lipolysis (where ERK1 / 2 activation is increased), the MAP kinase inhibitor PD98059 reduces TNF-alpha induced lipolysis in human cells in cell culture, and in contrast, the p38 kinase inhibitor SB203580 stimulates TNF-alpha induced lipolysis. The specification teaches only prophetically design of other MAPK inhibitors. There is a high level of unpredictability in the art for design of specific MAPK gene and protein inhibitors (note the references cited below in the enablement rejection) for the functions claimed in whole organisms. Although there are some general MAPK inhibitors known in the art, neither the specification nor the art teach design of specific inhibitors which would have the claimed functions *in vivo*. Specifically, design of an inhibitor for *in vivo*/pharmaceutical use has a high level of unpredictability compared to design of such an inhibitor for inhibition of a target in cell culture since the composition must specifically target via particular routes of administration all cites of intended action without causing toxicity and without degradation. The examples of inhibitors taught by the specification for use in cells in culture for reduction of lipolysis in cell culture cells induced in a particular way, do not correlate broadly to any possible inhibitor of any MAPK pathway composition for the functions claimed in any whole organism. Applicant thus would not have been in possession of the scope of claimed inhibitors at the time the invention was made.

3. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

See above for a description of the breadth of the claims and brief description of the inhibitors taught by the specification as filed.

There is a high level of unpredictability that the inhibitors taught in the specification as filed would function in a whole organism as claimed. One of the inhibitors taught in the specification as filed, PD098059, was shown to have no effect on noradrenaline-stimulated lipolysis as taught by Fryer et al. Thus, depending on the mechanism of stimulation of lipolysis, there is variability in the ability of known MAPK inhibitors to function to decrease lipolysis. Further, such known inhibitors are generally not specific for any one component of the MAPK pathway and are known to have many possible physiological changes in a whole organism. The other inhibitors taught in the specification were pre-administered to the cells in culture prior to stimulation of lipolysis by TNF-alpha. For these examples, there is no established correlation between administration of any possible inhibitor to cells in cell culture and administration to whole organisms as broadly claimed. Especially in the instant case of pre-treated cells, there is not a direct correlation to any complex disorder such as lipolysis, where an unknown number of variables are acting on causing the disorder (lipolysis can be caused by many different causes having different pathologies), for one skilled in the art to expect a treatment effect from looking at

the effects of pre-treated cell culture cells. Although several key components of MAPK pathways are known, the downstream effects of modulation of any known member of any MAPK pathway in any whole organism for treatment of lipolysis was not predictable at the time the invention was made. Specifically, since neither the specification nor the art teach inhibition of a specific component of a MAPK pathway having correlation to a direct reduction of a specific lipolysis condition in a whole organism, one skilled in the art would not have been able to practice the methods of treatment broadly claimed for treatment of any lipolysis in any whole organism with any inhibitor of any MAPK pathway component. Due to the lack of guidance in either the specification as filed for design of new inhibitors or how to use known inhibitors of any MAPK pathway gene for the therapeutic functions claimed would have required an undue amount of experimentation for one skilled in the art.

In regards to design of antisense, ribozyme or other gene inhibitors for instance, there is a further high level of unpredictability for design of such inhibitors which target a gene and function in a whole organisms for treatment purposes as instantly claimed. Note the following unpredictability in the art for antisense and related ribozyme and triplex arts:

The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes

with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)."

One of skill in the art would not accept on its face the successful delivery of any antisense designed to a known gene *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues,

(3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Souza et al. (IDS Reference AX), Klein et al. (U.S. Patent 6,255,059), Momose et al. (U.S. Patent 6,110,948), Marshall et al. (IDS Reference AM) and Davis et al. (IDS Reference AP).

Claims 15-16 are drawn to methods of screening for ERK 1 /2 and/or JNK activity in any individual that indicates that the individual has or is likely to develop a disease or condition caused by or contributed to lipolysis. Claim 18 is drawn to methods of identifying a compound which reduces TNF-alpha induced lipolysis comprising (I) isolating a compound which is an ERK 1 /2

and/or JNK inhibitor, and (ii) contacting an adipocyte with the compound of step (I) and TNF-alpha and determining the level of lipolysis.

Souza et al. are relied upon to teach methods of testing the effects of TNF-alpha and BRL 49653, an agonist of the PPAR-gamma2 receptor, on adipocyte lipolysis (see abstract). They teach the motivation for further analysis of the role of TNF-alpha stimulation in lipolysis and how TZDs block TNF-alpha lipolysis. They do not specifically teach looking for changes in ERK 1/ 2 and/or JNK expression for inhibition of lipolysis.

Klein et al. are relied upon to teach methods for screening G-protein coupled receptors for agonists and antagonists. They teach motivation for screening of MAPK pathways (see col. 4, line 32, for erk receptors, and col.15, lines 55-65 for screening receptors involved in JAK signaling) and also for therapeutic agents for treating lipolysis (see col. 1, line 57). They teach methods of screening in yeast and indirectly for use in whole organisms. They do not necessarily teach analysis of protein levels from a subject as a diagnosis.

Momose teach suppression of lipolysis in mice treated with diuretics such as sodium salicylate (col. 11, lines 16-17 and col. 13, lines 53-55). They teach screening such compounds as cancer therapeutics, but teach a suppression of lipolysis as a side effect. They do not specifically teach analysis of ERK 1/ 2 levels.

Marshall et al. and Davis et al. are further relied upon to teach methods of screening for compounds which modulate MAPK pathway components having potential therapeutic benefits. They do not necessarily teach the involvement of MAPKs in lipolysis.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to determine the activity of an ERK 1 or 2 and/or JNK in an individual for connection to lipolysis and screen for inhibitors of ERK 1 /2 or JNK to identify a compound which reduces lipolysis since the role of MAPK kinases such as ERK 1 /2 or JNK in connection to lipolysis was known in the art as taught by Souza et al., and methods of screening members of MAPK pathways were well-known in the art as taught by Klein et al, Momose et al., Marshall et al. and Davis et al. Klein et al. and Momose et al. further taught screening for agents involved in lipolysis.

One of ordinary skill in the art would have been motivated to study the effects of MAPK regulated pathways in connection to lipolysis, and further, screen for agents which modulate such pathway members, since the connection between lipolysis and MAPK pathway members was taught by Souza et al., Souza et al. specifically taught motivation for further deduction of the specific pathways involved in lipolysis, and Klein et al, Momose et al., Marshall et al. and Davis et al. all taught methods for screening MAPK pathway members for therapeutic agents involved in diseases such as lipolysis.

One of ordinary skill in the art would have had an expectation of success to (1) test a subject for elevated ERK 1 /2 and or JNK in an individual in conjunction with lipolysis since such methods of testing a subject were well-known in the art (methods of testing include identification of gene expression levels (Northern or Southern blots) or protein expression levels (Western

blots)) and (2) screen for agents which inhibit ERK 1 /2 or JNK since such methods of screening were well-known in the art as taught by Klein et al, Momose et al., Marshall et al. and Davis et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
September 12, 2001

ANDREW WANG
PRIMARY EXAMINER